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Mr. Stephen Johnson, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building, 1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Public comments on the HPV Test Plan for Isophthalonitrile

Dear Administrator Johnson:

The following comments on Syngenta's test plan for the chemical Isophthalonitrile are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

Syngenta Crop Protection, Inc. submitted its test plan on September 16, 2005, for the chemical Isophthalonitrile (CAS No. 626-17-5), referred to as IPN. This chemical is used as an intermediate in the production of agricultural fungicides. Syngenta has conducted a thoughtful analysis of the toxicity of IPN, and existing data for many SIDS endpoints were submitted. The sponsor intends to submit modeled data on environmental fate endpoints and, based on the acute fish toxicity characteristics of IPN, concluded that this chemical is not likely to pose a risk to aquatic invertebrates or plants. Although a separate developmental toxicity study was not located, Syngenta uses a weight-of-evidence approach to fill the data gap for developmental toxicity. We support this type of analysis and concur with Syngenta that no additional testing is required.

We appreciate Syngenta's efforts to conduct thoughtful toxicology in order to avoid additional animal testing and we would like to expand on Syngenta's conclusions. For a screening level program such as HPV, we believe there is sufficient evidence, based on the 28-day study and the 1-generation reproduction study, of fetotoxicity at 50 mg/kg/day IPN with a clear NOEL established at 25 mg/kg/day. Although there was a decrease in the number of live born pups and litter size, no obvious evidence of gross external teratogenicity was observed at a dose level that resulted in pup mortality. It might be expected that a separate, stand-alone developmental study would again show fetotoxicity/fetal lethality but no malformations. Furthermore, the genotoxicity profile of IPN was negative, indicating a lack of effects on cellular mechanisms. Moreover, adequate measures to protect workers from occupational exposure have already been established. The TLV for IPN is 5.0 mg/m^3. These data, when considered together,

suggest additional animal studies will not add to our knowledge of the toxicity of IPN and will only serve as a "check-the-box" exercise. This is consistent with the animal reduction measures set forth by the EPA in the *Federal Register* (December 2000), which states that HPV participants "may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested."

We submit that, in this instance, the entire knowledge of a chemical should be used to determine further planned testing. Syngenta does not provide any information on other chemicals with similar structural and toxicity profiles to IPN. Existing data from similar or analogous chemicals may be used to bridge data gaps for developmental toxicity of IPN.

We agree with Syngenta's proposal that no additional studies are needed to fulfill the SIDS data set for IPN and hope the suggestions we provided here will strengthen the test plan submission. Thank you for your attention to these comments. I may be reached at 202-686-2210, ext. 327, or via e-mail at *meven@pcrm.org*.

Sincerely,

Megha Even, M.S.
Research Analyst

Chad B. Sandusky, Ph.D.
Director of Toxicology and Research